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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/659,579 | 09/10/2003 | Anil Gulati | 27611/38545A | 4671 |

4743 7590 08/20/2008

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| EXAMINER | |
|---|---|
| CARTER, KENDRA D | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1617 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 08/20/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/659,579 | GULATI, ANIL | |
| | Examiner | Art Unit | |
| | KENDRA D. CARTER | 1617 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *15 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,9,13,15 and 19-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,9,13,15 and 19-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 15, 2008 has been entered.

The Examiner acknowledges the applicant's remarks and arguments of May 15, 2008 made to the office action filed December 20, 2007. Claims 1, 9, 13, 15 and 19-24 are pending. Claim 9 is amended.

In light of the amendments to claim 9, the 35 U.S.C. 112, second paragraph rejection is withdrawn.

The Applicant's arguments of the following 35 U.S.C. 103(a) rejection were found not persuasive and thus are maintained: 1) claims 1 and 9 as being unpatentable over Hughes et al. in view of Wu; and 2) claims 13, 15 and 19-24 as being unpatentable over

Hughes et al. in view of Wu as applied to claims 1 and 9 above and in further view of Woolf.

The above rejections have been modified to address the Applicant's arguments. The Examiner addressed the Applicants arguments after the rejections.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

**(1) Claims 1 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hughes et al. (US 2003/0040534 A1) in view of Wu (Expert Opinion on Therapeutic Patents, 2000, Vol. 10, No. 11, pp. 1653-1668).**

Hughes et al. teaches a compound that is an endothelin antagonist of ET-1 and ET-2, and are useful in treatment of conditions associated with increased ET levels and of all endothelin-dependent disorders such as for the treatment of Alzheimer's dementia (see page 2, paragraph 11, lines 1-5 and paragraph 18 in its entirety).

Hughes et al. does not teach the Applicant's elected endothelin antagonist compound bosentan.

Wu teaches that endothelins (ETs) exert their biological effects such as physiological and pathological conditions by binding to the $ET_A$ (binds ET-1 more than ET-2 or ET-3) and $ET_B$ (binds ET-1, ET-2 and ET-3 equally) (see page 1653, introduction in its entirety). The drug bosentan is an endothelin antagonist, particularly a mixed $ET_A/ET_B$ antagonist that has even been used in clinical trials (see page 1658, section 2.3, in particular.) Mixed $ET_A/ET_B$ antagonist are used to lower blood pressure, protect against ischaemia-induced neuronal degeneration (see page 1658-1661, $ET_A/ET_B$ balanced antagonists). $ET_A$ or mixed $ET_A/ET_B$ antagonist may be useful in the treatment of conditions such as prostate cancer, male erectile dysfunction and vascular remodeling. The debate continues over whether $ET_A$ or mixed $ET_A/ET_B$ antagonist are more therapeutically useful, but studies have shown that selective $ET_B$ antagonist compounds are not beneficial (see page 1665, column 1, lines 3-6 and 14-17).

Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious and motivated to provide the bosentan of Wu in the treatment of Alzheimer's dementia as taught by Hughes et al, because Hughes et al. teaches that Alzheimer's dementia is associated with increased ET levels and can be treated by providing endothelin antagonists having ET1/ET2 antagonist activity (which is directly associated with $ET_A$ and $ET_B$), whereas Wu teaches that

bosentan is a compound having known $ET_A/ET_B$ mixed antagonist activity. In other words, since the ETs must bind to the $ET_A$ and $ET_B$ receptors to exert their biological effects (such as Alzheimer's dementia), an antagonist of $ET_A$ and $ET_B$ inhibits the ability of the excess ET levels to exert their biological effect. Thus, one of ordinary skill in the art would have been motivated to provide the bosentan in the method of Hughes et al. with the expectation of providing a compound capable of treating Alzheimer's disease. Accordingly, claim 1 is obvious over the teachings of Hughes et al. and Wu.

In regards to the limitation of a administering to a human suffering from Alzheimer's disease, the Examiner reads the treatment of Alzheimer's dementia to meet this limitation. One who has Alzheimer's dementia has Alzheimer's disease and Hughes et al. treats this ailment, and thus treats Alzheimer's disease.

**(2) Claims 13, 15 and 19-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hughes et al. (US 2003/0040534 A1) in view of Wu (Expert Opinion on Therapeutic Patents, 2000, Vol. 10, No. 11, pp. 1653-1668) as applied to claims 1 and 9 above in further view of Woolf (US 5,466,696).**

The teachings of Hughes et al. and Wu are as applied to claims 1 and 9 above.

Hughes et al. and Wu do not teach a cholinesterase inhibitor, particularly the Applicant's elected compound tacrine as disclosed in claims 13 and 15. Hughes et al. and Wu also do not teach treatment regime disclosed in claims 19-24.

Woolf teaches tacrine and cytochrome P450 oxidase inhibitors and methods of use (see title). Clinical studies have been performed on patient's suffereing from Alzheimer's disease by utilizing tacrine (see column 1, lines 26-27).

Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious and motivated to provide the tacrine of Woolf in the endothelin antagonist Alzheimer's dementia treatment method of Hughes et al. in view of Wu, because Hughes et al. teach a method of treating Alzheimer's dementia. Thus, both Hughes et al. and Woolf teach treatments of Alzheimer's disease. Therefore, it is considered that one of ordinary skill in the art would have been motivated to provide tacrine in the Alzheimer's treatment method of Hughes et al. in view of Wu, with the expectation of providing a compound capable of treatment of the condition. Note it is considered that "[I]t is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980.)

Accordingly, claims 13 and 15 are considered to be obvious over the teachings of Hughes et al. in view of Wu in further view of Woolf

Regarding claims 19-24, Hughes et al. in view of Wu in further view of Woolf render obvious providing a combination therapy of the endothelin antagonist bosentan and the ACE inhibitor tacrine for the treatment of Alzheimer's disease. Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the treatment regime, such as by providing the therapeutic agents in the same or separate compositions, or by administering one of the compounds prior to the other, according to the guidance provided by Hughes et al. in view of Wu in further view of Woolf, to provide the desired Alzheimer's treatment. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.) It is furthermore noted that, regarding the order of administration as recited in claims 23-24, it has been held that merely changing the order of steps in a multi-step process is not a patentable modification absent a showing of unexpected results. *Ex parte Rubin* 128 USPQ 440 (POBA 1959.)

***Response to Arguments***

Applicant's arguments have been fully considered but they are not persuasive.

> The Applicant argues that $ET_A$ and $ET_B$ receptors act opposite to one another and give different responses. Hughes et al. ('534 publication) enables no more than $ET_A$ receptor antagonism and does not disclose which ET the compound antagonizes. Additionally, Hughes et al. does not provide guidance if the compounds inhibit or activate $ET_A$. Additionally, the present invention is not directed to a treatment of Alzheimer's disease, but to treating the adverse effects or symptoms resulting from Alzheimer's disease. The Wu reference does not remedy the Hughes et al. reference. The Wu reference does not teach or suggest the use of an endothelin antagonist in the treatment of Alzheimer's Disease. Thus, since the above arguments do not teach the present invention, the dependent claims 13, 15 and 19-24 should also be withdrawn.

The Examiner disagrees because although the $ET_A$ and $ET_B$ receptors can have different responses, it is also known that mixed $ET_A/ET_B$ antagonist are used to lower blood pressure, protect against ischaemia-induced neuronal degeneration (see Wu, page 1658-1661, $ET_A/ET_B$ balanced antagonists). Thus, positive responses are known from antagonizing both receptors. Additionally, Alzheimer's dementia (a symptom of Alzheimer's Disease) is a endothelin-dependent disorder (see Hughes et al., see page 2, paragraph 11, lines 1-5 and paragraph 18 in its entirety). Therefore upon antagonizing $ET_A$ and $ET_B$ receptors, one inhibits the action or response upon which the endothelin receptor will produce (i.e. Alzheimer's dementia). In regards to the Hughes et al. references teaching only antagonizism of the $ET_A$ receptor, Wu teaches that the debate continues over whether $ET_A$ or mixed $ET_A/ET_B$ antagonist are more therapeutically useful, but studies have shown that selective $ET_B$ antagonist compounds are not beneficial (see page 1665, column 1, lines 3-6 and 14-17). Thus regardless if the antagonism is only for the $ET_A$ or mixed $ET_A/ET_B$ receptor, one skilled in the art

would try the compound of Wu in hopes that the mixed $ET_A/ET_B$ antagonist would be effective to stop the response (Alzheimer's dementia) in which is associated with receptor. Thus, Hughes provides the teaching that antagonism of the ETs treats Alzheimer's dementia, and Wu teaches that antagonizing the ETs through the $ET_A$ or mixed $ET_A/ET_B$ receptors stops the responsive disorder associated with the ETs. Accordingly, the claims are obvious over the teachings of Hughes et al. and Wu.

***Conclusion***

No claims allowed.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KENDRA D. CARTER whose telephone number is (571)272-9034. The examiner can normally be reached on 7:30 am - 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/K. D. C./
Examiner, Art Unit 1617

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1617